# Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. N Engl J Med 2011;364:401-11.

**Supplemental online only materials**

METHODS

*Trial completion*

Following demonstration of high efficacy against EGL as shown in the current analyses, and with concurrence from the Data Safety Monitoring Board (DSMB), this study was terminated to allow for unblinding and vaccination of subjects who received placebo.

*Pathology panel*

The independent pathology panel provided histopathologic diagnoses for endpoint identification purposes. This panel was made up of 4 experts in the field of HPV pathology. To remove medico-legal pressures, the Pathology Panel members were informed that their diagnoses would not be used for primary medical management. They were told that if their consensus diagnosis was worse than that of the Program Central Pathology Laboratory, study sites would be notified. The experts comprising the panel were Robert Kurman, M.D., Brigitte Ronnett, M.D., Mark Stoler, M.D. and Alexander Ferenczy, M.D.

*Sample collection*

Swabs were collected separately from the penile, scrotal, perineal/perianal and anal areas. A metal nail file was used to gently rub the penile skin. A Dacron™ swab moistened with sterile saline was used to collect cellular debris generated and then placed into a container of sample transport medium (STM)(DIGENE, Gaithersburg MD). The procedure was repeated for the scrotum and perineal/perianal regions; each swab was placed in a separate STM vial. A fourth sample from the anal canal was obtained after a sample for cytology by inserting a moistened, non lubricated Dacron™ swab a distance of 2-3 centimeters into the canal. The swab was rotated while moving it in and out several times to retrieve cells.

*Milli Merck units*

The milli Merck unit (mMU) is an arbitrary unit of concentration assigned for each individual HPV type. The unit is calculated based on a serially diluted reference standard for each individual HPV type in the cLIA assay. It is important to note that the mMU/ml concentration for one HPV type is not equivalent to that of another HPV type.

Table S1. Subject Accounting for the Efficacy Analysis Populations by Vaccination Group

| | qHPV (N=2,032) | Placebo (N=2,033) | Total (N=4,065) | Population to Which Exclusion Category Applies | |
|---|---|---|---|---|---|
| | | | | PPE | NRT |
| **Number of Subjects who received at least 1 injection**[†] | 2,025 | 2,030 | 4,055 | | |
| **Eligible for the PPE Analysis Related to:** | | | | | |
| HPV 6/11 | 1,277 | 1,280 | 2,557 | | |
| HPV 16 | 1,327 | 1,308 | 2,635 | | |
| HPV 18 | 1,367 | 1,395 | 2,762 | | |
| **Ineligible for the PPE Analysis Related to:** | | | | | |
| HPV 6/11 | 748 | 750 | 1,498 | | |
| HPV 16 | 698 | 722 | 1,420 | | |
| HPV 18 | 658 | 635 | 1,293 | | |
| **Reason for Ineligibility**[‡] | | | | | |
| General protocol violation | 83 | 68 | 151 | x | |
| Received incorrect clinical material or dose amount | 5 | 1 | 6 | x | |
| Received non-study vaccination[§] | 30 | 23 | 53 | x | |
| Received immunosuppressives, IgG, or blood products | 13 | 12 | 25 | x | |
| With a history of immune disorder | 7 | 9 | 16 | x | |
| Diagnosed with HIV or is otherwise immunocompromised | 25 | 15 | 40 | x | |
| Received vaccine stored outside acceptable temperature range | 7 | 9 | 16 | x | |
| Subject prematurely unblinded | 1 | 0 | 1 | x | |
| Vaccination series not completed within 12 months[‖] | 7 | 7 | 14 | x | |
| Missed 2nd and 3rd vaccination | 89 | 101 | 190 | x | |
| Missed 3rd vaccination | 76 | 83 | 159 | x | |
| Without Day 1 serology results within acceptable day range[¶] | 5 | 8 | 13 | x | x |
| Without Day 1 swab PCR results within acceptable day range[#] | 169 | 161 | 330 | x | x |
| Without Month 7 swab PCR results within acceptable day range[‖#] | 244 | 221 | 465 | x | |
| HPV 6 or 11 Positive by Serology or PCR[††] | | | | | |
| At Day 1 | 194 | 191 | 385 | x | x |
| At or before Month 7 | 229 | 243 | 472 | x | |
| HPV 16 Positive by Serology or PCR[††] | | | | | |
| At Day 1 | 120 | 143 | 263 | x | x |
| At or before Month 7 | 164 | 192 | 356 | x | |
| HPV 18 Positive by Serology or PCR[††] | | | | | |
| At Day 1 | 77 | 70 | 147 | x | x |
| At or before Month 7 | 101 | 95 | 196 | x | |

[†] Subjects who did not receive at least 1 injection were excluded from all analysis populations.
[‡] Subjects are counted once in each applicable exclusion category. A subject may appear in more than one category.
[§] Includes live virus vaccines received within 21 days before or 14 days after study vaccination or inactivated or recombinant vaccines received within 14 days of study vaccination.
[‖] Among subjects who received all 3 vaccinations.
[¶] Includes subjects with a missing serum sample or missing cLIA results for ≥ 1 HPV type.
[#] Includes HM subjects who are missing at least two required swab samples or PCR results for ≥ 1 HPV type and MSM subjects who are missing at least three required swab samples or PCR results for ≥ 1 HPV type.
[††] Day 1 includes seropositivity or PCR positivity. Post-Day 1 includes PCR positivity only. Applies only to the analysis populations for the respective HPV type(s).
N = Number of subjects randomized to the respective vaccination group.

cLIA = Competitive Luminex immunoassay; HIV = Human immunodeficiency virus; HM = Heterosexual men; NRT = naive to the relevant type; HPV = Human papillomavirus; MSM = Men having sex with men; PCR = Polymerase chain reaction; PPE = Per-Protocol efficacy; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

Table S2. Baseline characteristics of subjects randomized by vaccination group

| | qHPV (N = 2,032) | Placebo (N = 2,033) | Total (N = 4,065) |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| **Sexual orientation** | | | |
| Heterosexual men | 1,731 (85.2) | 1,732 (85.2) | 3,463 (85.2) |
| Men having sex with men | 301 (14.8) | 301 (14.8) | 602 (14.8) |
| **Age (years)** | | | |
| Mean (SD) | 20.6 (2.0) | 20.5 (2.0) | 20.5 (2.0) |
| Median | 20 | 20 | 20 |
| Range | 16 to 26 | 15 to 27 | 15 to 27 |
| **Race/Ethnicity** | | | |
| Asian | 201 (9.9) | 205 (10.1) | 406 (10.0) |
| Black | 405 (19.9) | 400 (19.7) | 805 (19.8) |
| Hispanic American | 412 (20.3) | 423 (20.8) | 835 (20.5) |
| Native American | 1 (0.0) | 2 (0.1) | 3 (0.1) |
| White | 719 (35.4) | 712 (35.0) | 1,431 (35.2) |
| Other | 294 (14.5) | 291 (14.3) | 585 (14.4) |
| **Region** | | | |
| Africa | 268 (13.2) | 270 (13.3) | 538 (13.2) |
| Asia-Pacific | 180 (8.9) | 181 (8.9) | 361 (8.9) |
| Europe | 248 (12.2) | 248 (12.2) | 496 (12.2) |
| Latin America | 788 (38.8) | 787 (38.7) | 1,575 (38.7) |
| North America | 548 (27.0) | 547 (26.9) | 1,095 (26.9) |
| **Circumcision** | | | |
| Yes | 786 (38.7) | 757 (37.2) | 1,543 (38.0) |
| No | 1,244 (61.2) | 1,275 (62.7) | 2,519 (62.0) |
| **Lifetime number of male or female sexual partners at enrollment among non-virgins** | | | |
| 1 | 409 (20.2) | 448 (22.1) | 857 (21.1) |
| 2 | 384 (18.9) | 408 (20.1) | 792 (19.5) |
| 3 | 436 (21.5) | 447 (22.0) | 883 (21.8) |
| 4 | 425 (20.9) | 364 (17.9) | 789 (19.4) |
| 5 | 359 (17.7) | 347 (17.1) | 706 (17.4) |
| >5 | 2 (0.1) | 6 (0.3) | 8 (0.2) |
| **Number of new male or female sexual partners in the 6 months prior to study start among non-virgins** | | | |
| Unknown | 2 (0.1) | 0 (0.0) | 2 (0.0) |
| 0 | 1,149 (56.6) | 1,126 (55.5) | 2,275 (56.0) |
| 1 | 669 (33.0) | 685 (33.7) | 1354 (33.4) |

| | | | |
|---|---|---|---|
| 2 | 159 (7.8) | 158 (7.8) | 317 (7.8) |
| 3 | 30 (1.5) | 38 (1.9) | 68 (1.7) |
| 4 | 6 (0.3) | 8 (0.4) | 14 (0.3) |
| 5 | 2 (0.1) | 3 (0.1) | 5 (0.1) |
| >5 | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Percent calculated as 100*(n/N)

N = number of subjects randomized; n = number of subjects with the indicated characteristic; SD = Standard deviation.

Table S3. Analysis of efficacy in the naïve to the relevant type (NRT)* population against HPV 6/11/16/18-related (A) EGL (condyloma acuminata, PIN, and penile/perianal/perineal cancer) and (B) persistent infection and DNA detection

A. EGL

| | qHPV vaccine | | | | Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Cases | Person-Years at Risk | Rate | n | Cases | Person-Years at Risk | Rate | Observed Efficacy (%) | 95% CI |
| HPV 6/11/16/18-related EGL** | 1,775 | 13 | 4,262.8 | 0.30 | 1,770 | 52 | 4,186.0 | 1.24 | 75.5 | (54.3, 87.7) |
| By Sexual Orientation | | | | | | | | | | |
| HM Subjects | 1,501 | 11 | 3,810.8 | 0.29 | 1,497 | 42 | 3,731.8 | 1.13 | 74.4 | (49.3, 88.1) |
| MSM Subjects | 274 | 2 | 452.0 | 0.44 | 273 | 10 | 454.2 | 2.20 | 79.9 | (5.7, 97.9) |
| HPV 6/11/16/18-related EGL by HPV type | | | | | | | | | | |
| HPV 6-related EGL | 1,603 | 10 | 3,904.8 | 0.26 | 1,607 | 36 | 3,866.3 | 0.93 | 72.5 | (43.4, 87.8) |
| HPV 11-related EGL | 1,603 | 1 | 3,919.3 | 0.03 | 1,607 | 16 | 3,879.6 | 0.41 | 93.8 | (60.2, 99.9) |
| HPV 16-related EGL | 1,674 | 1 | 4,060.0 | 0.02 | 1,649 | 3 | 3,961.7 | 0.08 | 67.5 | (-305.1, 99.4) |
| HPV 18-related EGL | 1,713 | 2 | 4,146.9 | 0.05 | 1,715 | 1 | 4,107.4 | 0.02 | -98.1 | (-11587.0, 89.7) |
| HPV 6/11/16/18-related EGL by EGL type | | | | | | | | | | |
| Condyloma acuminata | 1,775 | 10 | 4,268.6 | 0.23 | 1,770 | 48 | 4,187.9 | 1.15 | 79.6 | (59.1, 90.8) |
| All PIN lesions | 1,775 | 4 | 4,274.0 | 0.09 | 1,770 | 4 | 4,223.5 | 0.09 | 1.2 | (-430.5, 81.6) |
| PIN 1 | 1,775 | 2 | 4,278.9 | 0.05 | 1,770 | 3 | 4,225.0 | 0.07 | 34.2 | (-474.7, 94.5) |
| PIN 2/3 | 1,775 | 2 | 4,276.1 | 0.05 | 1,770 | 1 | 4,223.9 | 0.02 | -97.6 | (-11555.6, 89.7) |
| Penile/perianal/perineal cancer | 1,775 | 0 | 4,280.9 | 0.00 | 1,770 | 0 | 4,225.4 | 0.00 | NA | NA |

* This population was DNA negative to HPV 6/11/16/18/31/33/35/39/45/51/52/56/58/59 at enrollment and seronegative for HPV 6/11/16/18 at enrollment and received at least one dose of vaccine or placebo. This population approximates a population of young men prior to sexual debut. NRT case counting began after day 1.
** Subjects are counted once in each applicable category. A subject may appear in more than one category.
n = number of subjects who have at least one follow-up visit after month 7; Rate = rate per 100 person years at risk; CI = confidence interval; EGL = external genital lesions with a diagnosis of condyloma acuminata, PIN, or penile/perianal/perineal cancer; PIN = penile/perianal/perineal intraepithelial neoplasia.
NRT = naïve to the relevant HPV type; this population consisted of subjects who received at least 1 dose of vaccine or placebo and were HPV-naïve (i.e., seronegative and PCR negative) to the vaccine HPV type being analyzed at day 1.

B. Persistent infection and DNA detection

| | qHPV vaccine | | | | Placebo | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Cases | Person-Years at Risk | Rate | n | Cases | Person-Years at Risk | Rate | Observed Efficacy (%) | 95% CI |
| **Persistent infection*** | | | | | | | | | | |
| HPV 6/11/16/18-related persistent infection | 1,669 | 58 | 3,865.2 | 1.50 | 1,664 | 175 | 3,697.2 | 4.73 | 68.3 | (57.1, 76.9) |
| By Sexual Orientation | | | | | | | | | | |
| HM Subjects | 1,410 | 46 | 3,481.0 | 1.32 | 1,405 | 136 | 3,328.9 | 4.09 | 67.7 | (54.5, 77.4) |
| MSM Subjects | 259 | 12 | 384.2 | 3.12 | 259 | 39 | 368.3 | 10.59 | 70.5 | (42.5, 85.9) |
| By HPV Type | | | | | | | | | | |
| HPV 6-related persistent infection | 1,513 | 16 | 3,594.0 | 0.45 | 1,510 | 64 | 3,525.1 | 1.82 | 75.5 | (57.1, 86.8) |
| HPV 11-related persistent infection | 1,513 | 3 | 3,614.9 | 0.08 | 1,510 | 22 | 3,576.4 | 0.62 | 86.5 | (55.1, 97.4) |
| HPV 16-related persistent infection | 1,578 | 29 | 3,703.2 | 0.78 | 1,545 | 76 | 3,567.4 | 2.13 | 63.2 | (42.9, 76.9) |
| HPV 18-related persistent infection | 1,610 | 13 | 3,799.6 | 0.34 | 1,614 | 42 | 3,744.0 | 1.12 | 69.5 | (42.1, 85.0) |
| **DNA detection** | | | | | | | | | | |
| HPV 6/11/16/18-related DNA detection | 1,669 | 253 | 3,669.7 | 6.89 | 1,664 | 372 | 3,547.9 | 10.49 | 34.2 | (22.7, 44.2) |
| By Sexual Orientation | | | | | | | | | | |
| HM Subjects | 1,410 | 193 | 3,313.1 | 5.83 | 1,405 | 299 | 3,192.2 | 9.37 | 37.8 | (25.2, 48.4) |
| MSM Subjects | 259 | 60 | 356.7 | 16.82 | 259 | 73 | 355.7 | 20.52 | 18.0 | (-16.9, 42.7) |
| By HPV Type | | | | | | | | | | |
| HPV 6-related DNA detection | 1,513 | 88 | 3,533.2 | 2.49 | 1,510 | 161 | 3,457.8 | 4.66 | 46.5 | (30.2, 59.2) |
| HPV 11-related DNA detection | 1,513 | 27 | 3,593.6 | 0.75 | 1,510 | 54 | 3,554.3 | 1.52 | 50.5 | (20.1, 70.0) |
| HPV 16-related DNA detection | 1,578 | 119 | 3,606.9 | 3.30 | 1,545 | 164 | 3,508.5 | 4.67 | 29.4 | (10.1, 44.7) |
| HPV 18-related DNA detection | 1,610 | 59 | 3,752.5 | 1.57 | 1,614 | 106 | 3,704.8 | 2.86 | 45.0 | (23.7, 60.7) |

*Persistent infection was defined as detection of the same HPV type (6, 11, 16 or 18) in an anogenital swab or biopsy specimen collected on ≥2 consecutive visits ≥6 (±1) months apart. Individuals with detection of HPV 6, 11, 16, or 18 DNA at ≥1 visit contributed to the DNA detection endpoint.

n = number of subjects who have at least one follow-up visit after day 1; Rate = rate per 100 person years at risk; CI = confidence interval.

Table S4. Analysis of efficacy against HPV 6/11/16/18-related persistent infection and DNA detection in the per-protocol efficacy (PPE) population

| | qHPV vaccine | | | | Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | Cases | Person-Years at Risk | Rate | n | Cases | Person-Years at Risk | Rate | Observed Efficacy (%) | CI[†] | P-value[‡] |
| **Persistent infection*** | | | | | | | | | | | |
| HPV 6/11/16/18-related persistent infection | 1,390 | 15 | 2,549.4 | 0.59 | 1,400 | 101 | 2,469.3 | 4.09 | 85.6 | (73.4, 92.9) | < 0.001 |
| By Sexual Orientation | | | | | | | | | | | |
| HM Subjects | 1,196 | 14 | 2,356.5 | 0.59 | 1,195 | 83 | 2,274.0 | 3.65 | 83.7 | (71.1, 91.5) | |
| MSM Subjects | 194 | 1 | 192.9 | 0.52 | 205 | 18 | 195.3 | 9.22 | 94.4 | (64.4, 99.9) | |
| By HPV Type | | | | | | | | | | | |
| HPV 6-related persistent infection | 1,239 | 4 | 2,320.2 | 0.17 | 1,238 | 33 | 2,296.6 | 1.44 | 88.0 | (66.3, 96.9) | |
| HPV 11-related persistent infection | 1,239 | 1 | 2,322.6 | 0.04 | 1,238 | 15 | 2,315.1 | 0.65 | 93.4 | (56.8, 99.8) | |
| HPV 16-related persistent infection | 1,290 | 9 | 2,382.4 | 0.38 | 1,264 | 41 | 2,312.9 | 1.77 | 78.7 | (55.5, 90.9) | |
| HPV 18-related persistent infection | 1,327 | 1 | 2,461.9 | 0.04 | 1,347 | 25 | 2,453.5 | 1.02 | 96.0 | (75.6, 99.9) | |
| **DNA detection** | | | | | | | | | | | |
| HPV 6/11/16/18-related DNA detection | 1,390 | 136 | 2,455.3 | 5.54 | 1,400 | 241 | 2,404.1 | 10.02 | 44.7 | (31.5, 55.6) | < 0.001 |
| By Sexual Orientation | | | | | | | | | | | |
| HM Subjects | 1,196 | 115 | 2,270.7 | 5.06 | 1,195 | 199 | 2,215.1 | 8.98 | 43.6 | (28.7, 55.6) | |
| MSM Subjects | 194 | 21 | 184.6 | 11.38 | 205 | 42 | 189.0 | 22.22 | 48.8 | (11.6, 71.2) | |
| By HPV Type | | | | | | | | | | | |
| HPV 6-related DNA detection | 1,239 | 51 | 2,292.4 | 2.22 | 1,238 | 99 | 2,267.7 | 4.37 | 49.0 | (27.9, 64.4) | |
| HPV 11-related DNA detection | 1,239 | 16 | 2,311.7 | 0.69 | 1,238 | 37 | 2,300.5 | 1.61 | 57.0 | (20.7, 77.6) | |
| HPV 16-related DNA detection | 1,290 | 62 | 2,337.7 | 2.65 | 1,264 | 103 | 2,287.8 | 4.50 | 41.1 | (18.5, 57.7) | |
| HPV 18-related DNA detection | 1,327 | 25 | 2,441.3 | 1.02 | 1,347 | 66 | 2,440.6 | 2.70 | 62.1 | (39.2, 77.1) | |

*Persistent infection was defined as detection of the same HPV type (6, 11, 16 or 18) in an anogenital swab or biopsy specimen collected on ≥ 2 consecutive visits ≥6 (±1) months apart. Individuals with detection of HPV 6, 11, 16, or 18 DNA at ≥1 visit contributed to the DNA detection endpoint.

[†] A 97.5% CI is reported for the HPV 6/11/16/18-related persistent infection endpoint. The CI reported for the HPV 6/11/16/18-related persistent infection endpoint differs from the other analyses due to the Hochberg multiplicity adjustment applied.

[‡] A p-value<0.025 (one-sided) corresponds to a lower bound of the confidence interval for vaccine efficacy greater than 20% and supports the conclusion that the vaccine is efficacious against the given endpoint. The Hochberg multiplicity adjustment has been applied to the p-value reported.

n = number of subjects who have at least one follow-up visit after month 7; Rate = rate per 100 person years at risk; CI = confidence interval.

Table S5. Breakdown of injection-site and systemic adverse experiences reported following any vaccination (incidence ≥1% in one or more vaccination group).

| | qHPV vaccine | | | | Placebo | | | |
|---|---|---|---|---|---|---|---|---|
| | All AE | | Vaccine related AE‡ | | All AE | | Vaccine related AE‡ | |
| | n | (%) | n | (%) | n | (%) | n | (%) |
| **Subjects in analysis population** | 2,020 | | | | 2,029 | | | |
| **Subjects with follow up** | 1,945 | | | | 1,950 | | | |
| **Injection-site related*** | 1166 | (59.9) | | | 1046 | (53.6) | | |
| Erythema | 304 | (15.6) | | | 275 | (14.1) | | |
| Pain** | 1113 | (57.2) | | | 991 | (50.8) | | |
| Pruritus | 22 | (1.1) | | | 24 | (1.2) | | |
| Swelling | 219 | (11.3) | | | 187 | (9.6) | | |
| **Systemic (by system organ class)†** | 615 | (31.6) | 274 | (14.1) | 613 | (31.4) | 284 | (14.6) |
| Gastrointestinal disorders | 125 | (6.4) | 35 | (1.8) | 120 | (6.2) | 33 | (1.7) |
| Abdominal pain - upper | 19 | (1.0) | 5 | (0.3) | 23 | (1.2) | 7 | (0.4) |
| Diarrhea | 40 | (2.1) | 10 | (0.5) | 36 | (1.8) | 13 | (0.7) |
| Nausea | 27 | (1.4) | 16 | (0.8) | 16 | (0.8) | 7 | (0.4) |
| General disorders | 160 | (8.2) | 109 | (5.6) | 169 | (8.7) | 122 | (6.3) |
| Fatigue | 13 | (0.7) | 6 | (0.3) | 19 | (1.0) | 15 | (0.8) |
| Pyrexia | 118 | (6.1) | 91 | (4.7) | 125 | (6.4) | 98 | (5.0) |
| Infections and infestations | 182 | (9.4) | 18 | (0.9) | 187 | (9.6) | 20 | (1.0) |
| Influenza | 42 | (2.2) | 9 | (0.5) | 44 | (2.3) | 7 | (0.4) |
| Nasopharyngitis | 44 | (2.3) | 3 | (0.2) | 50 | (2.6) | 5 | (0.3) |
| Pharyngitis | 22 | (1.1) | 1 | (0.1) | 20 | (1.0) | 0 | (0.0) |
| Upper respiratory tract infection | 27 | (1.4) | 3 | (0.2) | 20 | (1.0) | 4 | (0.2) |
| Injury, poisoning and procedural complications | 30 | (1.5) | 0 | (0.0) | 24 | (1.2) | 0 | (0.0) |
| Musculoskeletal disorders | 61 | (3.1) | 21 | (1.1) | 50 | (2.6) | 15 | (0.8) |
| Nervous system disorders | 207 | (10.6) | 121 | (6.2) | 231 | (11.8) | 138 | (7.1) |
| Dizziness | 19 | (1.0) | 12 | (0.6) | 18 | (0.9) | 14 | (0.7) |
| Headache | 179 | (9.2) | 107 | (5.5) | 207 | (10.6) | 119 | (6.1) |
| Respiratory disorders | 70 | (3.6) | 25 | (1.3) | 68 | (3.5) | 8 | (0.4) |
| Pharyngolaryngeal pain | 38 | (2.0) | 14 | (0.7) | 37 | (1.9) | 2 | (0.1) |
| Skin and subcutaneous disorders | 26 | (1.3) | 10 | (0.5) | 31 | (1.6) | 14 | (0.7) |

*Days 1-5 following vaccination; all injection site adverse experiences are considered vaccine-related.
**P value for risk difference between vaccine and placebo groups = 0.001
†Days 1-15 following vaccination.
‡ Determined by the investigator to be possibly, probably, or definitely related to the vaccine.

Although a subject may have had two or more adverse experiences, the subject is counted only once within a category.
Percentages are calculated based on the number of subjects with follow-up.

Figure S1. Subject accounting in Protocol 020

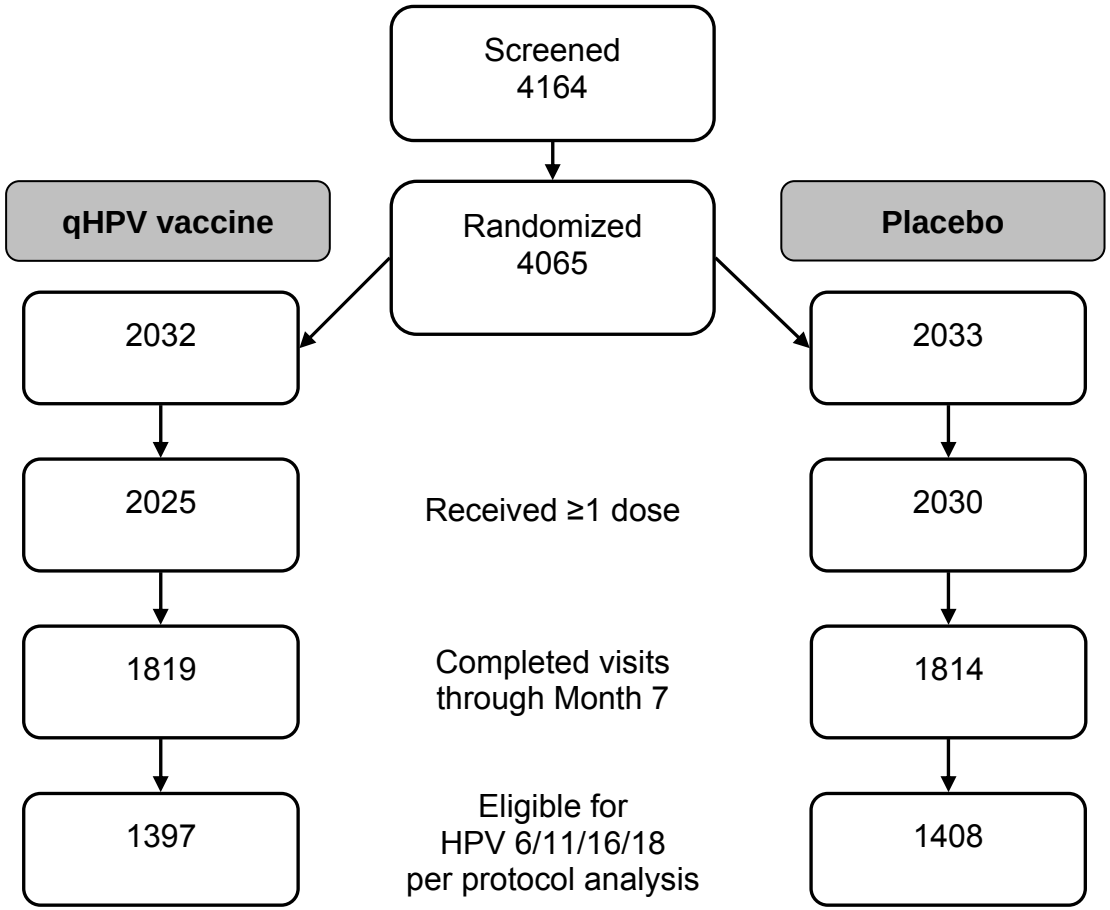
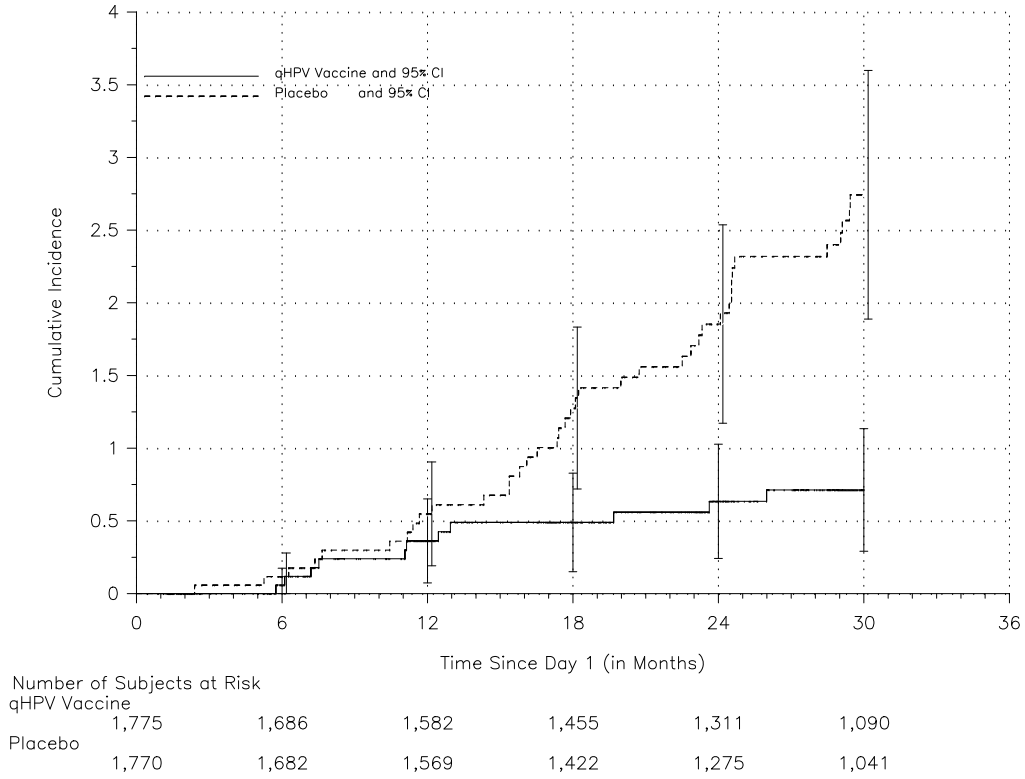


Figure S2. Analysis of time to 6/11/16/18-related EGL in the NRT population




EGL = external genital lesions with a diagnosis of condyloma acuminata, penile/perianal/perineal intraepithelial neoplasia, or penile/perianal/perineal cancer; Cumulative incidence = Cumulative incidence per 100 person years; qHPV vaccine = quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine.